Initially, applicants recall that the Examiner has vigorously argued that the claims of the instant application are unpatentable as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to practice the invention. Specifically, the Examiner has argued that there exists unpredictability in the relevant art such that undue experimentation would be required to practice the claimed methods with a reasonable chance of success. See Papers 9 and 13. The Examiner has now taken a completely contrary position, instead arguing that the claimed methods of the present invention are taught by the prior art. Applicants note that such inconsistency is not well-founded.

Further, as described herein below, applicants submit that (1) motivation to combine the references as proposed by the Examiner is not found in the prior art, and (2) at the time of filing the present application, the proposed combination did not offer a reasonable chance of success.

The Examiner relies on Lederman, Armitage, and Aruffo as describing the use of gp39 antagonists (anti-CD40L antibodies and/or soluble CD40L variants) to induce T cell tolerance. Office Action, at pages 2-3. However, the Examiner correctly notes that neither Lederman, Armitage, nor Aruffo teach co-administration of autoantigen expressing cells, as recited in the pending claims. Office Action, at page 3, ¶ 2. As the basis for the rejection of claims under § 103(a), the Examiner suggests that this deficiency is provided by Eynon (which teaches that B cell presentation of antigen in the absence of help can elicit antigen-specific T cell anergy), Beschorner (which teaches induction of tolerance by depletion and re-population of thymic APCs), and Cobbold (which teaches CD4 specific antibodies to support T cell immunity). Specifically, the Examiner suggests that at the time of the present invention, one skilled in the art would have been motivated to combine administration of autoantigen expressing cells and gp39 antagonists because both treatments contribute to long term antigen non-responsiveness. Office Action, at page 3, ¶ 6.

The studies by Eynon suggest a role for B cells as antigen-specific, tolerizing antigen-presenting cells. Eynon's experimental results are limited to a demonstration of tolerance to a foreign antigen in animals pre-treated with the same antigen, modified so as to be targeted to B cells. Eynon suggests, but does not show, that B cells *may* also

maintain peripheral tolerance in a similar manner. Thus, Eynon's studies reveal an *in vivo* role for B cell-mediated tolerance, which is not predictably extrapolated to a successful method of treatment via administration of autoantigen expressing cells.

The patent to Beschorner teaches a method for inducing antigen-specific immune tolerance by depletion of resident thymic APCs and re-population of thymus with APCs expressing the antigen for which tolerance is sought. The method of Beschorner require that the thymus is depleted of APCs by administering an immunosuppressive agent. Beschorner's teachings are therefore limited to therapeutic administration of antigen and APCs only in the context of thymic depletion. Thus, contrary to the suggestion of the Examiner, Beschorner does support a general conclusion that APCs can be administered therapeutically to induce tolerance.

In addition, Beschorner does not teach administration of any immunosuppressant in combination with APCs, but rather only APC-depleting immunosuppressants, which are required as an additional step of the Beschorner method and are not required to perform the methods of the present invention.

With respect to Cobbold, the findings disclosed therein are limited to induction of tolerance to a self-antigen by administering a CD4 antibody, optionally in combination with an immunosuppressive agent. The teachings of Cobbold are limited to methods that employ CD4 and do not teach or suggest the use of gp39 antagonists.

Based on the foregoing arguments, the cited references do not suggest administration of autoantigen-presenting cells in combination with *any* immunosuppressant, and specifically a gp39 antagonist, to thereby treat autoimmune disease. As described further below, the cited references also do not motivate such a combination.

The Examiner further contends that a skilled artisan would be motivated to administer any immunosuppressant in combination with autoantigen-presenting cells, on the basis that each agent contributes to long term antigen non-responsiveness in the treatment of autoimmunity. Office Action, at page 3, ¶ 6. Applicants respond that the Examiner's proposed combination of teachings is implausible as having no reasonable chance of success. In particular, the term "immunosuppressant" is a generic term that encompasses agents having substantially different *in vivo* effects (*e.g.*, thymic depletion of

APC's or interference of CD4 signaling). Combination of substantially different individual therapies to thereby result in another successful therapy cannot be predicted. Indeed, for the treatment of autoimmunity, there is significant concern that inhibition of immune responses also unreasonably increases susceptibility to infection. Thus, the mere existence of a variety of therapies generally directed to immunosuppression does not motivate any particular combination based on an anticipation of success.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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